DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-558/S-049
NDA 50-643/S-010

Glaxo Wellcome, Inc.
Attention: Ann N. Stokely, M.S.P.H.
Product Director, Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Stokely:

Please refer to your supplemental new drug applications dated May 14, 1998, received May 15, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for

NDA 50-558/S-049 for ZINACEF® (sterile cefuroxime sodium)
NDA 50-643/S-010 for ZINACEF® (cefuroxime sodium injection)

We acknowledge receipt of your submission(s) dated March 9, 2000. Additionally, reference is made to the facsimile dated August 17, 1999, wherein the Division requested changes to the package insert.

These supplemental new drug applications provide for the following changes:

PRECAUTIONS

1. The subheader "**General**" has been added immediately following the header for the **PRECAUTIONS** section.
2. The following statements were added to the **General** subsection under **PRECAUTIONS**:
   "Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous Vitamin K administered as indicated."
3. The **Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy** subsections under **PRECAUTIONS** have been revised to conform with the statements found in the Ceftin® labeling as follows:
   a) "**Carcinogenesis, Mutagenesis, Impairment of Fertility**: Although lifetime studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic activity was found for cefuroxime axetil in the mouse lymphoma assay and a battery of bacterial mutation tests. Positive results were obtained in an *in vitro* chromosome aberration assay, however, negative results were found in an *in vivo* micronucleus test at

doses up to 10 g/kg. Reproduction studies in mice at doses up to 3200 mg/kg per day (3.1 times the recommended maximum human dose based on mg/m^2) have revealed no impairment of fertility.
Reproductive studies revealed no impairment of fertility in animals."

b) "**Pregnancy: Teratogenic Effects**: Pregnancy Category B. Reproduction studies have been performed in mice at doses up to 6400 mg/kg per day (6.3 times the recommended maximum human dose based on mg/m^2) and rabbits at doses up to 400 mg/kg per day (2.1 times the recommended maximum human dose based on mg/m^2) and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed."

ADVERSE REACTIONS

1. Seizure has been added to the **Neurologic** subsection under "**Postmarketing Experience with ZINACEF® Products**".
2. The following statement concerning seizures should remain in the **Cephalosporin-class Adverse Reactions** subsection:

> "Several cephalosporins, including ZINACEF®, have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION**). If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated."

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted March 9, 2000.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, these submissions should be designated "FPL for approved supplement NDA's 50-558/S-049 and 50-643/S-010." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Cdr. R. Grant Hills, Regulatory Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research